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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/929,771	08/14/01	LUM	R 96,877-V1

HM22/1022

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EXAMINER	
BERCH, M	
ART UNIT	PAPER NUMBER
1624	4

DATE MAILED: 10/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/929,771	LUM ET AL.	
	Examin r	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48-49, 68-72 are rejected under 35 U.S.C. 102(b) as being anticipated by Regnier.

See example 2, 27 and other purine examples which do not have a heterocycle attached at the 2-position. These correspond to claim 3 with $R_3 = NR_4 R_5$, and R_5 = optionally substituted lower alkyl. The compounds are anticancer agents.

Claims 48-53, 56-57, 61, 64, 68-76 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 97/20842.

Note page 6 of the translation of French 2741881, which table appears on page 7 of WO 97/20842. Many of these species avoid the proviso, e.g. species 6 and 10 in Table 1. The same biochemical property is disclosed. The claims in this case are broader than the disclosure of the parent and hence are only entitled to the date of 8/1/97. See the various lettered points in the description rejection above; the same issues would apply to the parent --- this material isn't in 08/692012.

Claims 48-53, 56-57, 61, 64, 68-76 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 97/16452.

Note formula I and species therein which deal with 6- (substituted anilino) species. The utility is the same.

Claims 48-53, 56-57, 61, 64, 68-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Norman.

The species named in the second paragraph of page 7431, column 2 is not subject to the proviso as it is a substituted benzyl. The utility is the same.

Claims 48-49, 51, 56, 76 are rejected under 35 U.S.C. 102(b) as being anticipated by McAfee.

See the list at Column 4 of the species, and note species 4, 5 and the 4th from last, all substituted in the 2-position.

Claims 48-49, 51, 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Seyama.

See compounds 39 and 35. In the latter, this corresponds to R_3 = substituted heteroaralkyl.

The rejections made in the parent over Kaneko and WO 93/17020 are not included because R_2 = substituted heterocyclic and hydroxy-cyclopentyl respectively is no longer permitted. The rejection made in the parent over Breshears is not included because R_2 = H is no longer permitted. The rejections made in the parent over Bader and Liotta are not included because R_1' = halogen is no longer permitted.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48-53, 56-57, 61, 64, 68-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vesely.

The reference discloses olomoucine, which the proviso removes from claim 1. However, the 2-(hydroxymethyl amino), or the 6-(2-phenethylamino) and other choices would all be chain homologues, with one carbon fewer or one carbon more respectively. However, it has long been established that this type of difference --- varying the size of a chain --- constitutes a form of homology, and is a fact of very close structural similarity, rendering the homolog obvious. See *In re Shetty*, 195 USPQ 753; *In re Wilder*, 195 USPQ 426 and *Ex Parte Greshem*, 121 USPQ 422, all of which feature a compound with a C_2 link rejected over a compound with a C_1 link. Similarly, *In re Chupp*, 2 USPQ2d 1437 and *In re Coes*, 81 USPQ 369 have a C_1 link unpatentable over prior art showing C_2 link. Note also *In re Schaub,* 190 USPQ 324, 326, where compounds with C_5 and C_6 chains were called "adjacent homologs in the classic sense". *Ex parte Ruddy*, 121 USPQ 427 has a C_3 link unpatentable over a C_1 link. *Ex parte Nathan*, 121 USPQ 349 found the insertion of a C_2H_4 link obvious. In all of these cases, the variation was found to be obvious on the basis of close structural similarity; no secondary teaching was employed. In addition, the 6-(1-phenethylamino) choice would be the same as the prior art, just with an extra methyl on the α carbon of the benzyl. Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the

motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood,* 199 USPQ 137; *In re Hoke,* 195 USPQ 148; *In re Lohr,* 137 USPQ 548; *In re Magerlein,* 202 USPQ 473; *In re Wiechert,* 152 USPQ 249; *Ex parte Henkel,* 130 USPQ 474; *Ex Parte Fischer* 96 USPQ 345; *In re Fauque,* 121 USPQ 425; *In re Druey,* 138 USPQ 39. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. See also MPEP 2144.09, second paragraph. The utility is the same.

Claims 1-2, 8-9, 37-46 are rejected under 35 U.S.C. 102(a) as being anticipated by De Azevedo.

The reference is from the January 1997 issue. It discloses roscovitine, shown in column 20. The same biochemical property is disclosed. The same issue arises, except that instead of the 2-(hydroxymethyl amino), the hydroxymethyl-butyl would be one carbon larger (C_5) and thus avoids the proviso. .

Claims 48, 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moschel.

Note Table 1, compounds 4c, 4a, 4e, 4f. These differ only in that they lack the 9-methyl of the claims. However, such a feature is explicitly taught by the reference; see claim 2 which is drawn exactly to that feature.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. "Heteroalkyl" is indefinite; there is no such thing. Is it a alkyl substituted by a heterocycle, e.g. pyridyl-methyl? An alkyl interrupted by a heteroatom, such as methoxymethyl? An alkyl substituted by a heteroatom, e.g. chloromethyl? Whatever choice is selected must be supported by the specification.
2. If this means heterocyclic, then it is still indefinite. What is the size of the ring? What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated?
3. Also, claim 65 has "heterocyclyl" a term which does not appear in claim 48.
4. The same problem exists for "cycloheteroalkyl", except that a cycle must be present somewhere. Would this be something like cyclohexyl-oxy-methyl, which would be a cyclic group, which substitutes a heteroatom, which substitutes an alkyl?
5. The term "acyl" is indefinite. Does this embrace acids of S? P? As? What does the stem look like, i.e. if the acyl is e.g. RC(O), what is R?

6. The phrasing "disease state characterized by cell proliferation" surely does not reflect applicants' intent. Cell proliferation is a normal body process, and is going to be involved in a large proportion of all disease states. For example, any infection will involve the body proliferating new cells to fight the infection, so this covers all infectious disorders. Many failures of regulatory mechanisms in the body involves the body proliferating either too little or too much of some cell.
7. "Amido" is indefinite. There is no way of knowing whether applicants intend just carboxylic acid amides, or whether sulfonic, phosphonic, etc amides are intended. But even if carboxylic acid amido is intended, the term is undefined. Such a molecule generically has the formula RC(O)NR'R". One of the R choices will be used to attach, depending on whether the amido is C- or N-bound. Which end is intended for attachment? What is the nature of the other two R groups? Can the two of them together form a ring, and if so, of what type?
8. In claim 39, "graft-host disease" is defective; presumably, "host-vs.-graft disease" is intended.
9. In R_1', optionally substituted with what?
10. The use of "alkylthiol" e.g. ethanol, as a substituent in R_2 and R_3 is impossible. This is a molecule, and hence has no free valence, and so cannot be a substituent.
11. Similarly, all the R_3 choices in claim 63 are molecules, not moieties.
12. Claim 74 is garbled. IκB-α is not an inhibitor; it's the name of a kinase
13. Claims 51-76 are all improperly dependent on canceled claims.
14. A number of the claim 71 disorders are not considered a "cell proliferative disorder," assuming that dependence in claim 70 is intended by the word order.

Gout is a manifestation of hyperuricemia. Crystals of sodium urate cause acute inflammatory arthritis. It is not treated with antiproliferative agents, but instead with anti-inflammatory agents. Multiple Sclerosis is of unknown cause, although it is suspected of being of immunological origin. It is not characterized by cell proliferation, but is a destruction of the preformed myelin. Treatment does not involve standard antiproliferative agents, but instead involves the use of corticosteroids, and even that is for symptom relief; it does not treat the underlying disorder. Similarly, lupus (SLE is assumed) arise from hyperactivity of the immune system. "graft-host" (presumably, "host-vs.-graft disease" is intended) is not normally considered a cell proliferation disease, but is more or less an expected response to foreign lymphocytes, when the body is unable to reject them. Type I diabetes is a disorder of the carbohydrate mechanism caused by little or no endogenous insulin. Rheumatoid arthritis is generally classified as an autoimmune disorder. Restinosis is not a disorder per se, and certainly not a cell proliferation disorder, but is a generic term covering recurrent narrowing, including narrowing of almost any type. It is more a term that describes a physical condition.

15. Claim 50 ends with a comma.
16. In eighth from last line of claim 48, there is a semicolon after "or" which makes no sense.
17. Also, the second "or" on that line resumes what list? Both previous lists, the R_3 definition, and the R_4/R_5 definition lists have already been closed with their own

"or" words, so this material, starting at seventh from last line of claim 48, has no clear role.

18. The second choice on page 4, line 1, is not correct because it includes the N, which is not part of R_1'.

19. In the proviso, "R_3 is not lower alkyl ... substituted by ..." does not make sense. R_3 is not permitted to be substituted lower alkyl in the first place. Judging by the original provisos, it is assumed that applicants really intended something along the lines of "R_3 is not -NHQ, where Q is lower alkyl ... substituted by ...", which would exclude olomoucine, and that assumption was used in determining the prior art rejections.

In regard to some of the above points, e.g. points 1, 3, the examiner notes the "definitions" provided beginning on page 11. This material cannot be relied upon because it is grossly defective and thus useless. For example, the definition of alkoxy on page 12 says OR where R is aryl, (thus e.g. phenoxy), acyl (thus acyloxy), etc, which are not alkoxy groups at all. Similarly terms such as alkyl are permitted to have rings, contrary to their definition. The definition of alkylthio includes methyl-SO_2; such a group is an alkylsulfonyl, not an alkylthio. Moreover, the definitions given conflict with their actual use in the claims. Thus, original claim 1 had "substituted hetaryl" but according to the definition, this includes "heterocycle" which already permits substitution. The definition of "cycloheteroalkyl" (a self-contradictory term) is already covered by heterocycle, yet both terms appear in the e.g. R_1 definition. The definition of substituted ("functional groups") is completely open-ended, as virtually anything can be a "functional group". The definitions are also recursive, in that they define terms in

terms of themselves. Thus, "heterocycle" is defined in terms of rings which ca be substituted by heterocycle. That just starts the definition all over again.

Claim 68 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is no practical way to determine what the scope of claim 68 is. It is entirely possible that the claim covers all known diseases. Determining whether a given disease responds or does not respond to such inhibition will surely involve undue experimentation. Suppose that a given Inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how

many different inhibitors must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, there are thousands of known cell cycle kinase inhibitors, affecting a number of different kinases. One would have to test all of them to determine that a given disease does not fall within the claim.

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claims 48-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A. "-O-" for X is clearly new. Oxo, the original language, is an oxygen atom double bonded to a carbon. Applicants have removed the carbon entirely by using –O-.

B. The replacement of "thio" with "mercapto" in R_3 is new matter. The term "thio" is a generic one, indicating the presence of sulfur in some form. As a substituent, it has no one single generally accepted meaning. There could be intended thioxo (=S) or mercapto (-SH). It can also denote replacement by S of some other atom (normally, oxygen or carbon) as in "thioalkoxy", where O is replaced by S. Perhaps some term which began with "thio", like thiophene was intended. The selected choice must be supported by the specification, showing that one of ordinary skill in the art, reading the specification, would have been sure that this is what was originally intended.

C. The choice of "substituted aralkyl" in R_1' lacks description in the specification. While many other R_1' choices are specified as being optionally substituted, this one is not.

D. The same problem occurs in R_2; aralkyl is not permitted to be substituted.

E. The proviso lacks description. Even a negative limitation requires description, *Ex Parte Grasselli,* 231 USPQ 393. The claims originally had several provisos, but the new one does not appear to be on the original list, nor does it appear to be a combination of any of several of the original provisos. In addition, note point 19 above.

F. The claim has been expanded because some of the original provisos have been removed. For example, page 11, line 3, last word, bars a circumstance when the 6-position substituent is something other than benzylamino, viz., 3-methylbutylamino. That circumstance is no longer barred.

G. The "alkoxy" of page 2, line 7 is broader than the specification, which has "lower alkoxy" at page 13, line 3, 16, etc. Likewise in the R_3 definitions.

H. The "ethynyl" of page 2, line 8 is broader than the "acetylene" of page 13, line 3, as the latter permits only two carbons. Likewise at page 2, line 10. Likewise in the R_3 definitions.

I. The substituent list at page 2, line 8 is not supported for the choice of heteroarylalkyl, because several items on that line (amino, amido, carboxy, etc) are not present on page 14, lines 8-10. Likewise in the R_3 definitions.

J. The last line of claim 48 lacks description in the specification. Where did this come from?

K. The utility in claim 68 lacks description in the specification. Where does the specification say that these compounds can be used to treat any disease alleviable by treatment with any cell cycle kinase inhibitor. That literally covers treatment of every disease which is treatable by any cell cycle kinase inhibitor, even one unrelated to the ones here, even inhibitors which have no effect on CDK2, and even ones which are vastly more potent than the compounds here, and even compounds which have additional properties which are actually responsible for the potency.

L. The last choice of "substituted heteroalkyl" in R_1' lacks description in the specification. While many other R_1' choices are specified as being optionally substituted, this one is not.

M. The scope of claim 70 lacks description in the specification. See point 6 above.

N. The choice of substituted heteroaralkyl in R_2 and in R_3 lacks description in the specification. See page 5, line 9, and page 6, line 2. The paragraphs list substituted choices for certain ones, but not for this one.

Claim 70 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A proliferative disorder is anything that causes any abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as certain types of restenosis, vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, clonal proliferative disorders including the various Myelodysplastic Syndromes such as Refractory anemias, certain types of abnormal wound healings, different types of abnormal angiogenisis, pulmonary fibrosis, macular degeneration, myeloproliferative disorders such as primary polycythemia and myleofibrosis, and rheumatoid arthritis. There is no such thing that an agent which is effective against such disorders generally, since they are so diverse, nor is there any reason to think that such an agent could be made to work.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving

such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Claim 72 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim sets forth the treatment of cancer generally. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Further, this specification fails to actually name which cancer(s) these compounds would be expected to be effective against. Since there are no established

anticancer agents structurally related to these compounds, this lack of disclosure places an improper burden on the public to figure out how to use the compounds. The sole testing done in this regard appears on page 50. At 3 dosage regimens, the tested species met the minimum standard of efficacy, T/C = 130. However, compound 3 is by far the most potent as noted below. In terms of the ability to inhibit cell proliferation, the next most potent compound tested had only 1/6 its potency and hence would not be expected to pass even this crude screening test with L1210.

Claim 75 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement for the scope of "inflammation" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two

fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the

formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as Salmonella, Staphylococcus, Streptococcus (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent. Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

In gout, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Pseudogout, sometimes referred to as calcium pyrophosphate disease (CPPD), is inflammation caused by calcium pyrophosphate (CPP) crystals. It is treated with nonsteroidal anti-inflammatory drugs , corticosteroids and Colchicine.

Sinusitis is the inflammation of the mucosal lining of one or more sinuses. It commonly accompanies upper respiratory viral infections and in most cases requires no treatment.

Pharyngitis (tonsillitis) is an inflammatory illness of the mucous membranes and underlying structures of the throat (nasopharynx, uvula, and soft palate). The illness can be caused by bacteria, viruses, mycoplasmas, fungi, and parasites, and uncertain causes, especially Streptococcus pyogenes, adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, and Mycoplasma pneumoniae. Similarly, Osteomyelitis is the inflammation of bones, generally caused by bacteria (most commonly Staphylococcus Aureus). The disease can be caused by fungi or viruses. Dacryoadenitis, an inflammation of the tear gland, can arise from infectious

mononucleosis, mumps, gonorrhea, or influenza. Conjunctivitis (pink eye) is inflammation of the conjunctiva and can be caused by many microorganisms, including staphylococci, Haemophilus influenzae, streptococci, gonococci, and viruses such as adenoviruses. Treatment in all of these cases, when possible, is thus to the underlying infectious agent.

Rheumatoid arthritis is an inflammatory bone disease causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-18 and IL-18, and IFN- .

Pneumonia is an inflammation of the lungs that can be caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), bacteria, fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents.

Other inflammations in the respiratory system include CF, adult respiratory distress syndrome, asthma and bronchitis.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g. drugs may be used to improve the heart's ability to contract and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot

foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris, syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is an inflammation of the outer covering of the brain and spinal cord. It can be caused by virtually any known infectious agent. Thus, if it is caused by Haemophilus influenzae or Neisseria meningitis, the antibiotic derivative rifampin would be used.

Encephalitis is an inflammation of the brain itself. It is most often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also take the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids is an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything which obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation,

straining at stool, diarrhea, dysentery, rough toilet paper, uncleanliness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the body's exterior. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when Neisseria gonorrhoeae is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially Candida albicans), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone

and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder which is associated with the presence of Mycobacterium paratuberculosis. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as Candida albicans, dentures, chemotherapy and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to Lactobacillus capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Rhinitis is inflammation of the mucous membrane of the nose.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is

generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, Diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from Helicobacter pylori. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee string), acute allergic

contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrowing hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions of the skin frequently show some degree of inflammatory response. Acne's inflammation is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus Propionibacterium acnes, which populates the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), which are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those which are not, including chronic

abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Claims 68-74 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The compounds are disclosed to be CDK2 inhibitors. There is no reason to think that one of ordinary skill in the art could, without undue experimentation, treat such difficult disorders with such compounds. Note the following:

I. References of record do not support such a notion. Glab(1994) does not mention therapeutic utility. Others present use only as a possibility to be achieved by developing much better compounds. For example, Vesely (1994) says, "It is possible that, through its specificity, olomoucine may lead to a compound which will preferentially inhibit the proliferation of certain tumor cells." Olomoucine is excluded by proviso from the claims. This shows that basic research is still required to obtain the necessary selectivity. Abraham (1995) says that "olomoucine may constitute a lead compound for the design of new anti-tumor agents." Similarly, Schultz-Gahmen (1995) referring to its results, says it "should prove useful in modifying and improving the lead compound." But, a lead

compound is one which is not actually ready for use; it is by its nature something which needs to be modified by additional research.

II. Although olomoucine itself is not potent enough to be effective, the testing presented in Table 6 established that these compounds are either less effective as CDK2 inhibitors than olomoucine, or are not effective to actually inhibit cell proliferation even in this crude test. Indeed, a number of species displayed no measurable in either test. The specification says that cell proliferation inhibition has an IC(50) of "preferably less than 0.5 g/ml" which is a reasonable standard, but not a single species even came close to meeting that standard. Indeed, only one species (the 8th on page 48, "compound (3)") even tested below 10. Even on this very simple in vitro test, the results show that the compounds as a whole are ineffective.

III. The inclusion of gout in claim 71 makes no sense at all. Patients with gout are normally told to avoid high purine foods, in order to reduce uric acid secretion.

IV. Lupus (SLE) and MS in claim 71 are among the most intractable nervous system disorders, evidence that the skill level in this art is very low relative to difficulty of task. No one has been able to treat these with CDK2 inhibitors.

V. As set forth in point 6 above, the claim 70 language is extremely broad. No pharmaceutical could possibly have such a range.

VI. It is noted that this case discloses an additional property (not present in original parent 08/692012) which "some of the compounds of this invention" (page 3, line 8) have, viz, inhibition of IκB-α kinase. However, it is noted that a) it is unclear which compounds actually have this property, aside from the ones tested on page 56 and b)

this is one of many kinases about which relatively little is known and c) it is not asserted that any of the utilities in these rejected claims are connected to this property.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 8, 10, 14-16, 18, 20, 44-48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5866702. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims here are just broader versions of those of the grandparent case.

Specification

The parentage is incorrect, as it has the parent as a CIP of 08/692012, which is not the case.

The abstract is objected to as much too general, as it gives no idea what the substituents are.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

October 19, 2001